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09/806,413	03/30/2001	Shigeru Yamamoto	Q63731	8678

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/806,413	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the corresp ndence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *5-10 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 1-20 are pending in the application.

Applicants' election with traverse of Group I, claims 1-4 and 11-14, drawn to an enzyme and a method for producing a non-recombinant enzyme in Paper No. 9, filed 03/12/02 is acknowledged.

Lack of Unity

1. Applicants traverse the restriction requirement on the grounds that the claimed enzyme is derived from a microorganism, thereby distinguishing the claimed enzyme from that of the cited prior art (Ijima et al. *J Agric Food Chem* 46:1712-1718). Applicants argue that because the claimed enzyme is distinct from that of the prior art, the polypeptide of Group I, polynucleotide of Group II, and method of Group III relate to a single general inventive concept, and therefore, claims 5-10 and 15-20 should be co-examined with the claims of Group I. Applicants' argument has been fully considered and is not found persuasive. While the polypeptides of claims 1 and 2 *are* limited to polypeptides derived from microorganisms, the polypeptides of claims 3 and 4 *are not so limited*. Therefore, claim 3, drawn to a polypeptide having at least one deletion, addition, insertion or substitution of the polypeptide of SEQ ID NO: 8 and having an activity to release saccharides from a disaccharide glycoside, were known in the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-10 and 15-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Specification/Informalities

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Diglycosidase Isolated From *Aspergillus fumigatus*". See MPEP § 606.01.

Claim Objections

3. Claims 1, 3, 11, and 13 are objected to because of the following informalities: the term "in disaccharide unit", is grammatically incorrect and should be replaced with, for example, "in a disaccharide unit". Appropriate correction is required.

4. Claim 13 is objected to as reciting non-elected subject matter. Specifically, the claim recites "[t]he method... ...according to claim 10". It is suggested that applicants remove the non-elected subject matter from the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to enzymes and polypetides. The claims read on products of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated". See MPEP § 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1-3 and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 1 (claim 2 dependent therefrom) is indefinite in the recitation of "microorganism-derived enzyme". It is unclear from the claims and the specification as to the meaning of the term "microorganism-derived". The term has a plurality of meanings and can be interpreted as, for example, isolated from a microorganism or produced by a microorganism. It is suggested that applicants replace the term "A microorganism-derived enzyme" with, for example, "An enzyme isolated from a microorganism".

8. Claims 1, 3, 11 (claim 12 dependent therefrom), and 13 are confusing in the recitation of "having an activity to act upon a disaccharide glycoside to release saccharides from said disaccharide glycoside in disaccharide unit". It is unclear from the specification and the claims as to the meaning of the term. Based upon the specification at page 4, lines 3-9, it appears the term is meant to be interpreted as an enzymatic activity wherein a disaccharide is cleaved from a polysaccharide, i.e., diglycosidase activity. However, it appears from the specification at page 4, lines 9-16, the enzyme also has the activity of cleaving disaccharides into monosaccharides. It is suggested that applicants clarify the intended enzymatic activity of the claimed enzyme. Based upon the definition provided in the claim, the examiner has interpreted the term "having an activity to act upon a disaccharide glycoside to release saccharides from said disaccharide glycoside in disaccharide unit" as enzymatic activity wherein a disaccharide is cleaved from a polysaccharide, i.e., diglycosidase activity. If the examiner's interpretation of the claim is incorrect, Applicant should so state and clarify the record.

9. Claim 2 is indefinite in the recitation of "analogous disaccharide glycoside". It is noted that applicants have provided a definition for analogous disaccharide glycosides at the bottom of page 6 of the specification as follows: "disaccharides having glucose on the aglycon side" and have provided examples of analogous disaccharide glycosides as apiofuranosyl-beta-D-glucopyranoside and arabinofuranosyl-beta-D-glucopyranoside. However, it remains unclear as to how "analogous" to β-primeveroside a disaccharide glycoside must be to be included in the scope of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 11 (claim 12 dependent therefrom), and 13 (claim 14 dependent therefrom) are directed to: a genus of microorganism-derived enzymes with diglycosidase activity (claim 1) and optionally wherein the enzyme releases a disaccharide from β-primeveroside and/or an analogous disaccharide glycoside (claim 2); a genus of polypeptides having at least one deletion, addition, insertion or substitution of the polypeptide of SEQ ID NO: 8 and having diglycosidase activity (claim 3); a method of producing a genus of enzymes with diglycosidase activity by culturing a genus of microorganisms (claim 11) and optionally wherein the genus of microorganisms is selected from Aspergillus, Penicillium, Rhizopus, Rhizomucor, Talaromyces, Mortierella, Cryptococcus, Microbacterium, Corynebacterium, and Actinoplanes (claim 12), and optionally wherein the nutrient medium contains a genus of substances that induce production of an enzyme having diglycosidase activity (claim 13). The specification teaches the structure of only two representative species of such diglycosidases, a single representative species of such microorganisms, and a single representative species of such substances, i.e., the mature diglycosidase of SEQ ID NO:8 and the inactive precursor diglycosidase of SEQ ID NO:10 obtained by culturing Aspergillus fumigatus strain IAM 2046 in the presence of a saccharide. Moreover, the specification fails to describe any other representative species of diglycosidases, microorganisms, and substances by any identifying characteristics or properties other than the functionality of being

diglycosidases, microorganisms, or substances that induce production of an enzyme having diglycosidase activity. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

11. Claim 1-3 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO:8 and a method of production thereof by culturing *Aspergillus fumigatus* strain IAM 2046 with or without a saccharide for induction of expression of said polypeptide, does not reasonably provide enablement for *all* microorganism-derived enzymes with diglycosidase activity (claim 1), and optionally wherein the enzymes release a disaccharide from β-primeveroside and/or *any* analogous disaccharide glycosides (claim 2); *all* polypeptides having at least one deletion, addition, insertion or substitution of the polypeptide of SEQ ID NO: 8 and having diglycosidase activity (claim 3); a method of producing *all* enzymes with diglycosidase activity by culturing *any* microorganism (claim 11), or *any* microorganism of the genus Aspergillus, Penicillium, Rhizopus, Rhizomucor, Talaromyces, Mortierella, Cryptococcus, Microbacterium, Corynebacterium, and Actinoplanes (claim 12), and optionally wherein the nutrient medium contains *any* substance that induces production of an enzyme having diglycosidase activity (claim 13). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3, 11 (claim 12 dependent therefrom), and 13 (claim 14 dependent therefrom) are so broad as to encompass *all* diglycosidases, methods of producing diglycosidases by culturing *any*

microorganism in a nutrient medium that contains *any* substance that induces production of an enzyme having diglycosidase activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of diglycosidase enzymes, microorganisms, and substances broadly encompassed by the claims. However, in this case the disclosure is limited to the polypeptide of SEQ ID NO:8 and a method of production thereof by culturing *Aspergillus fumigatus* strain IAM 2046 with or without a saccharide for induction of expression of said polypeptide.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass *all* diglycosidases, methods of producing diglycosidases by culturing *any* microorganism in a nutrient medium that contains *any* substance that induces production of an enzyme having diglycosidase activity because the specification does not establish: (A) regions of the protein structure of SEQ ID NO:8 which may be modified without affecting diglysodidase activity; (B) the general tolerance of the polypeptide of SEQ ID NO:8 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues of the polypeptide of SEQ ID NO:8 with an expectation of obtaining the desired biological function; (D) methods of isolating *any* diglycosidase from *any* organism or microorganism as

methods of isolating other diglycosidases using salt precipitation and chromatography or hybridization probing as disclosed at pages 46, 47, and 52-54 of the specification require sufficient structural homology to the polypeptide of SEQ ID NO:8 or the polynucleotide of SEQ ID NO:9 for their application and are therefore not useful for structurally unrelated but functionally identical polypeptides and encoding polynucleotides; (E) a rational and predictable scheme for using any substance for induction of a diglycosidase; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including *all* diglycosidases, methods of producing diglycosidases by culturing *any* microorganism in a nutrient medium that contains *any* substance that induces production of an enzyme having diglycosidase activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-3 and 11-14 are rejected under 35 U.S.C. 102(b) as anticipated by ~~or, in the alternative, under 35 U.S.C. 103(a) as obvious over~~ McCormack et al. (Biotechnol Lett 13:677-682, 1991). Claim 1 is drawn to an enzyme isolated from a microorganism with an ability to cleave a disaccharide unit from a

disaccharide glycoside polysaccharide. Claim 2 limits the disaccharide glycoside polysaccharide of claim 1 to β-primeveroside or an analogous disaccharide glycoside polysaccharide. Claim 3 is drawn to a polypeptide having at least one deletion, addition, insertion, and substitution and having an ability to cleave a disaccharide unit from a disaccharide glycoside polysaccharide. Claim 11 is drawn to a method of producing the enzyme of claim 1 by culturing a microorganism in a medium and collecting the enzyme. Claim 12 limits the microorganism to a genus of microorganisms selected from *Aspergillus, Penicillium, Rhizopus, Rhizomucor, Talaromyces, Mortierella, Cryptococcus, Microbacterium, Corynebacterium*, and *Actinoplanes*. Claim 13 limits the medium of claim 11 to a medium containing a substance that induces enzyme production and claim 14 limits the substance of claim 13 to a saccharide.

McCormack teaches a method of producing an enzyme having chitobiase activity by culturing *Talaromyces emersonii* grown in a medium containing chitin for enzyme induction (pages 677, abstract and 678, bottom). Following enzyme production, McCormack teaches isolating the enzyme by centrifuging the cells and collecting the supernatant comprising the enzyme for further analysis (page 678, middle). This anticipates claims 1-3 and 11-14 as written.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. Claims 1-3, 11, 13 and 14 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Harman et al. (US Patent 6,020,540). Claims 1-3, 11, 13, and 14 are drawn to enzymes and methods of producing enzymes as described above.

Harman teaches an enzyme isolated from *Trichoderma harzianum* strain P1 having chitobiase activity (column 2) wherein the enzyme cleaves a dimeric unit from chitin (column 4). Harman teaches (Example I) a method of producing the chitobiase enzyme in Modified Richard's medium containing crab shell chitin (column 5) followed by a method of isolating the produced chitobiase by column chromatography. While Harman does not specifically teach adding crab shell chitin for induction of the chitobiase, one of ordinary skill in the art at the time of the invention would have recognized that the chitin was added to the Modified Richard's medium for chitobiase induction. Therefore, claims 1-3, 11, 13, and 14 are anticipated by or at least *prima facie* obvious in view of Harman.

Conclusion

14. All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

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